Using Deep Learning with Spatial Transformations to Predict Protein-Ligand Binding

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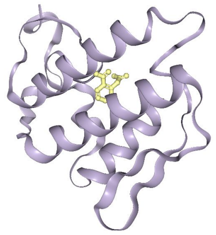
Introduction - Drug Discovery

- Time Consuming - Expensive - Labor Intensive
- Protein-Ligand Binding is Important for Drug Discovery
    - 90% of drugs on market act on proteins*
- Protein: molecules essential for body functions
- Ligand: molecule that binds to a protein, i.e. drug



1OXR - Aspirin binding

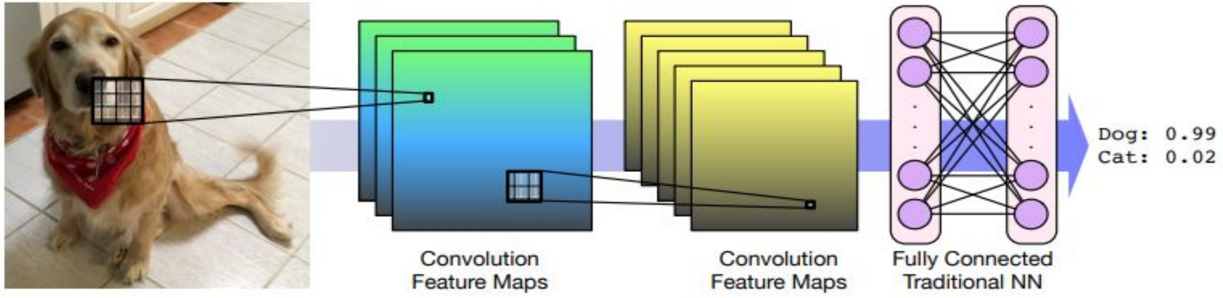
Causes anti-inflammatory effects

Singh RK, Ethayathulla AS, Jabeen T, Sharma S, Kaur P, Singh TP.J Drug Target. 2005 Feb; 13(2):113-9.

*Rask-Andersen, et al., Trends in the exploitation of novel drug targets. Nature Reviews Drug Discovery, 10:579-590, Aug. 2011

Introduction - Convolutional Neural Networks

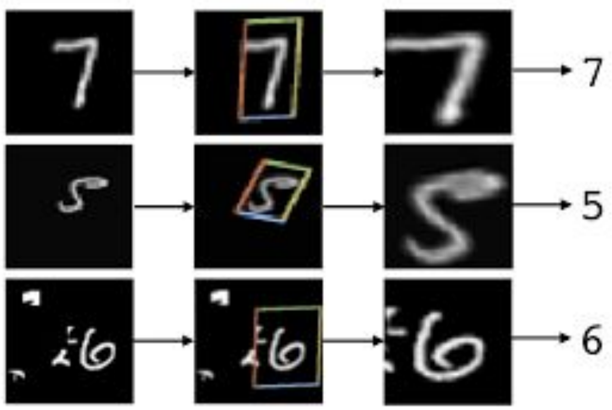
- Deep Learning Neural networks
    - Commonly applied to analyzing visual imagery
    - Learns features of the image as “filters” or “feature maps"
    - Each additional layer allows learning at a higher level features



Ragoza, M. et al. Protein-Ligand Scoring with Convolutional Neural Networks. J. Chem. Information and Modeling. 942-957, April. 2017

Introduction - Spatial Transformer Networks

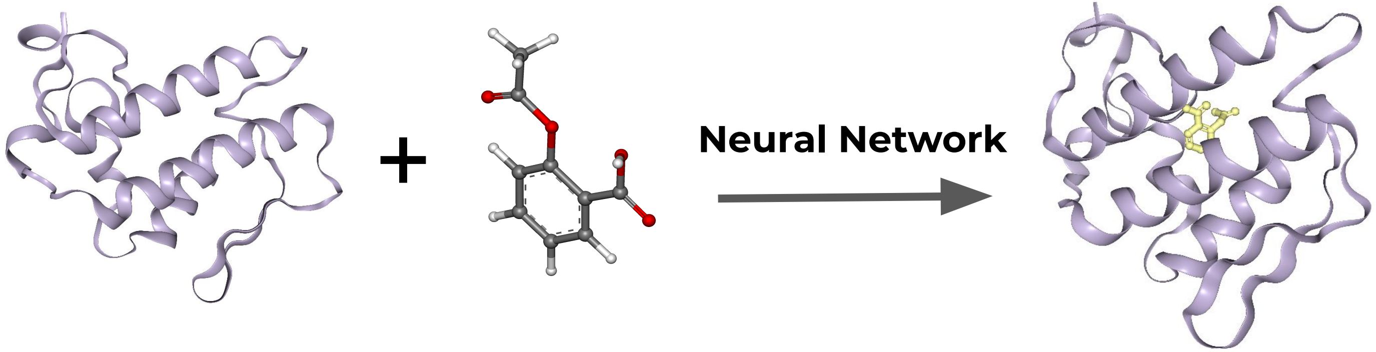
- STNs module incorporated into CNN
- Manipulates data in multiple dimensions
- Spatially transforms data
- Resilient to perturbation
  - translation, rotation, dilation, warping



Jaderberg, M. et al. “Spatial Transformer Networks”. Feb. 2016

Introduction - Can we do it?

Question: can neural networks predict protein-ligand binding after rigid body transformations?

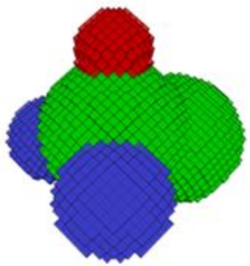


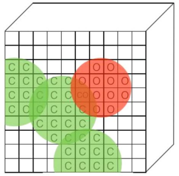
1OXR Aspirin 1OXR-Aspirin

Method - Ligand Voxelization and Perturbation

3D Voxelization

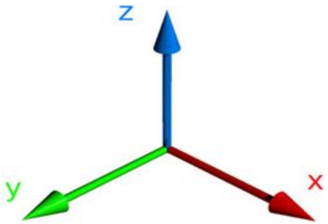
- Represents structures in cartesian coordinates
- Atoms represented as voxels





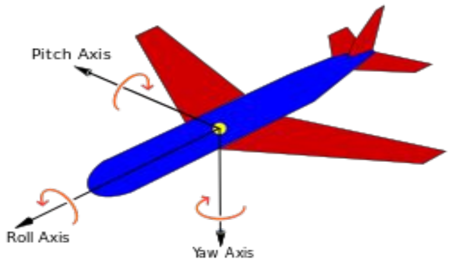
Translation

- Translated along x, y and z axis
- Error measured in angstroms

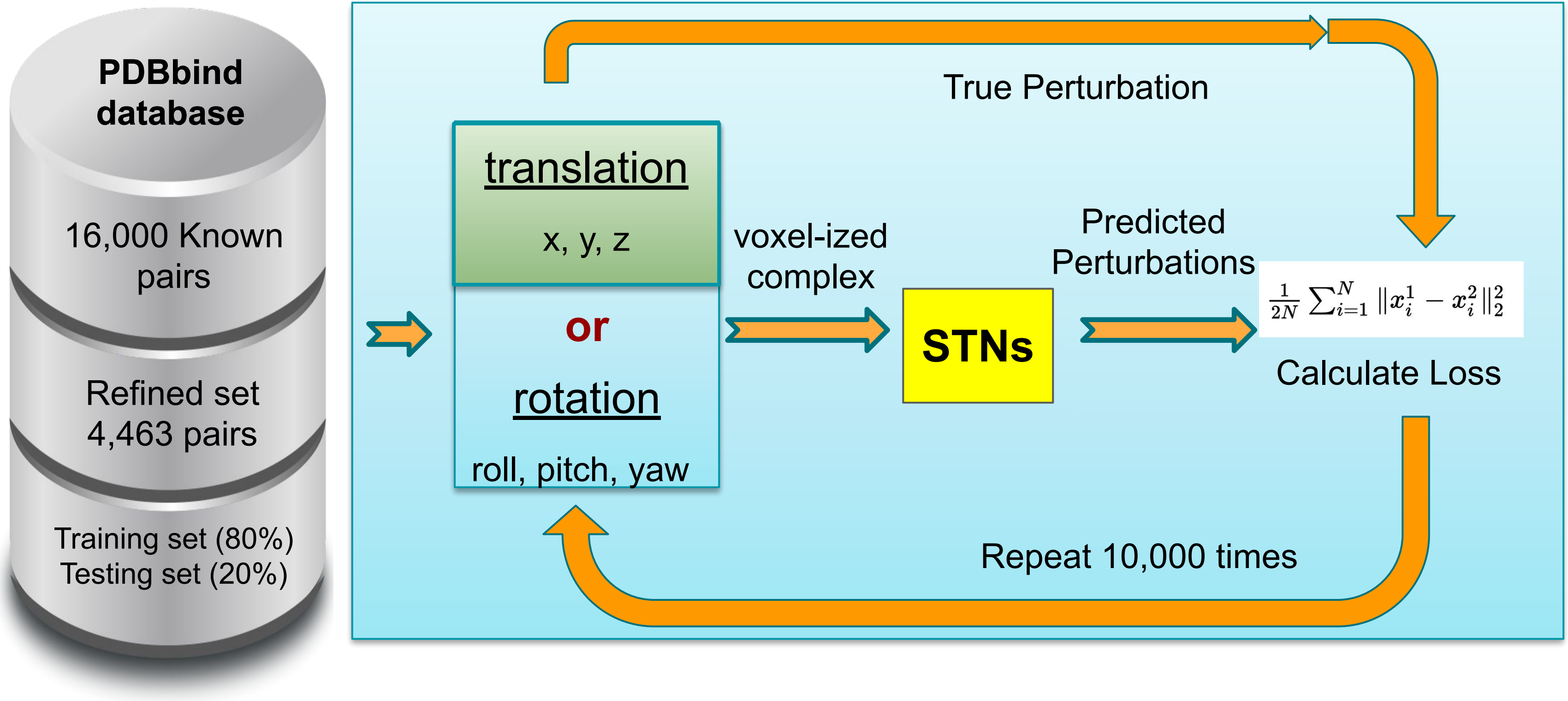


Rotation

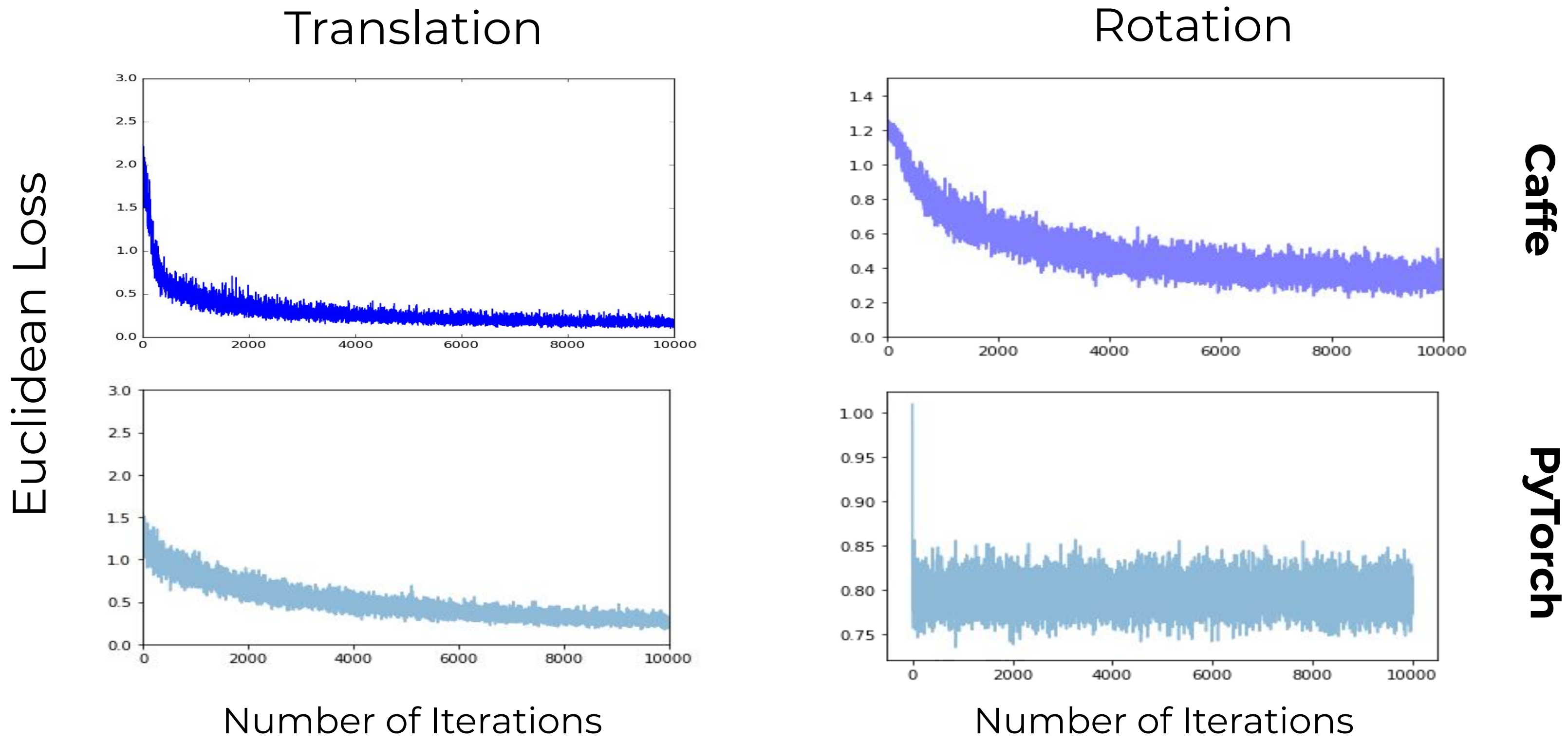
- Translated along roll, pitch and yaw
- Error measured in radians



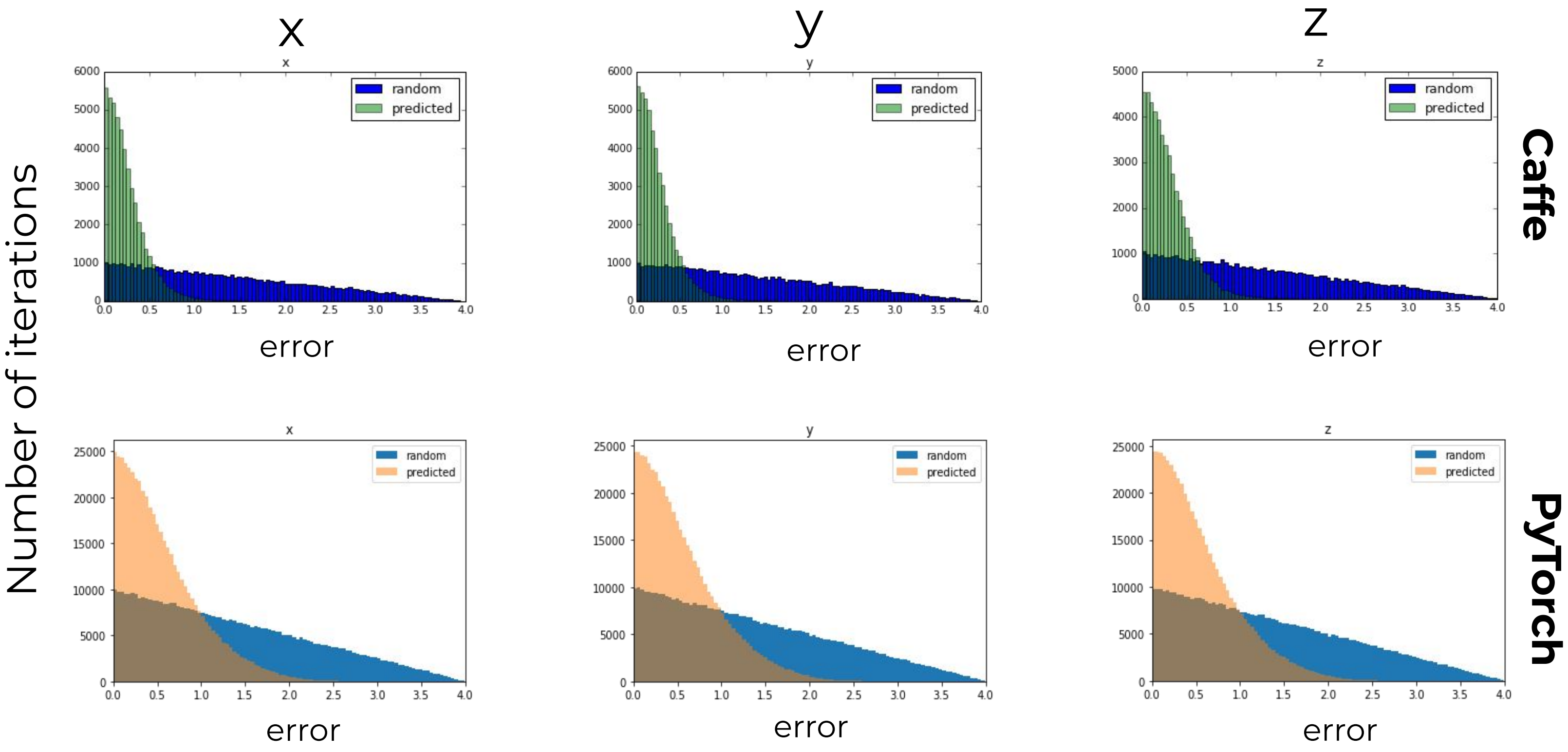
Methods - Pytorch and Caffe Outline



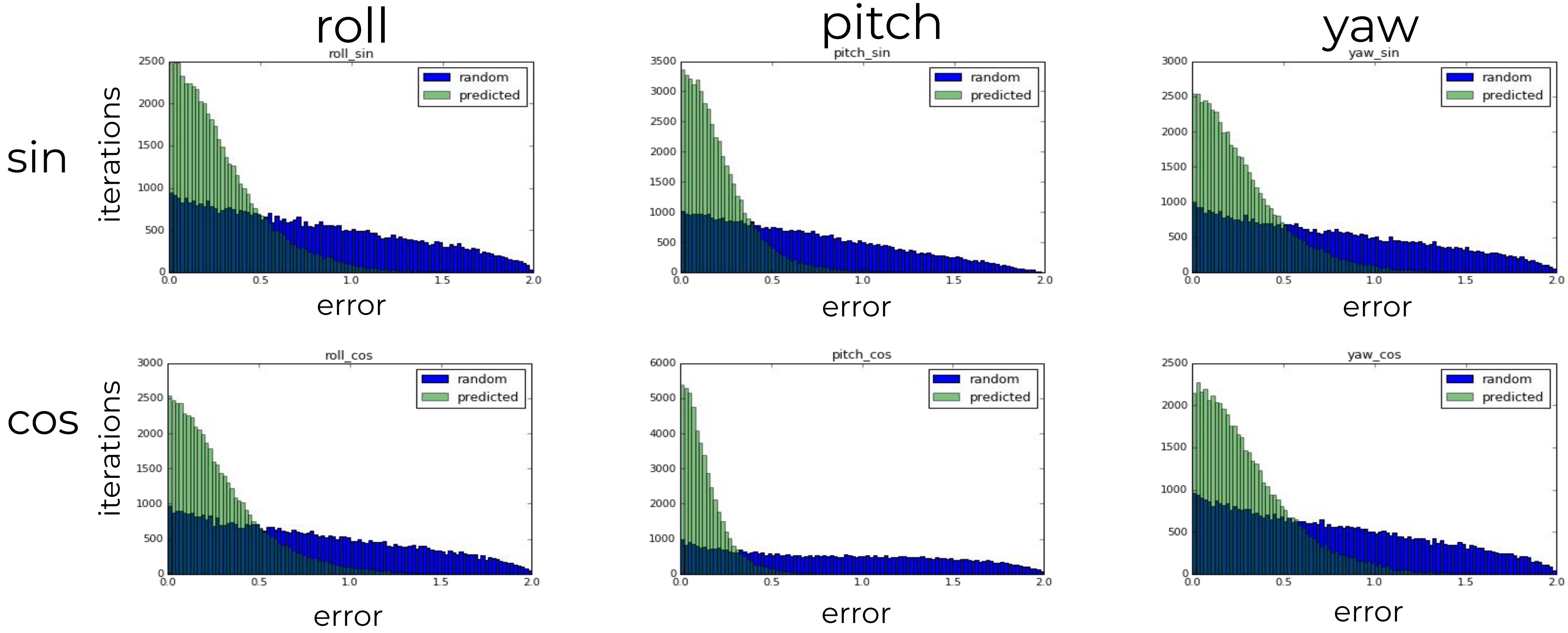
Results - Loss Convergence: Caffe vs PyTorch



Results - Prediction Accuracy: Translation



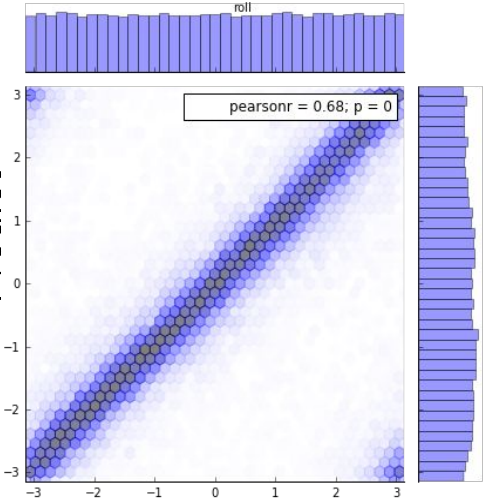
Results - Prediction Accuracy: Rotation-Caffe



Results – Correlation between predicted and true values for rotational models: Caffe

roll

Predict

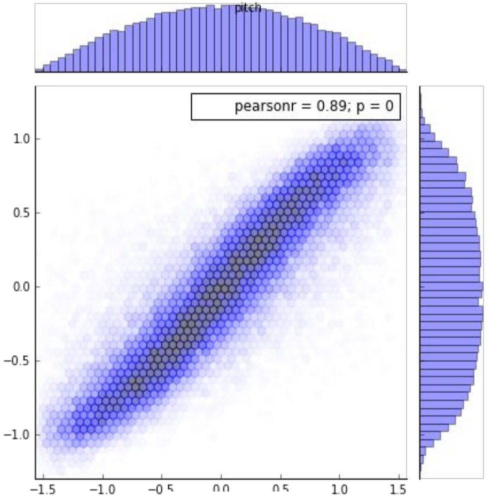


True

Pearson r = 0.68, p = 0

pitch

Predict

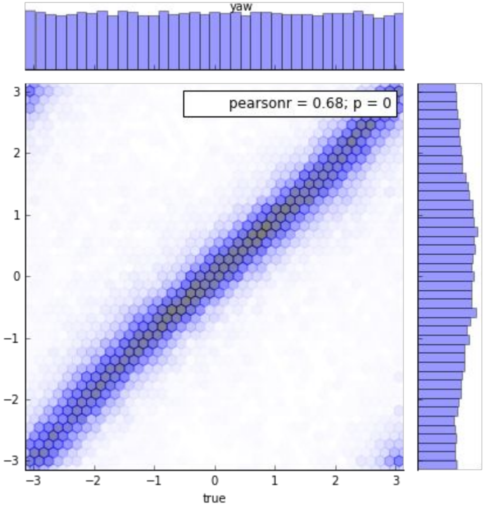


True

Pearson r = 0.89, p = 0

yaw

Predict



True

Pearson r = 0.68, p = 0

Results - Summary of Pearson R

		Roll		Pitch		Yaw		X		Y		Z	
		Train	**Test**	**Train**	**Test**	**Train**	**Test**	**Train**	**Test**	**Train**	**Test**	**Train**	**Test**
Caffe	**2 Angstrom Translation**	-	-	-	-	-	-	0.96	0.96	0.96	0.96	0.96	0.96
	Rotation	0.68*	0.68*	0.89	0.89	0.69*	0.68*	-	-	-	-	-	-
PyTorch	**2 Angstrom Translation**	-	-	-	-	-	-	0.86	0.86	0.85	0.85	0.86	0.86
	Rotation	0	0	0	0	0	0	-	-	-	-	-	-

*Indicates biased Pearson R value

Conclusions

- STNs are able to converge indicating their learning capacity. Caffe model seems to work better than PyTorch model
- STNs are able to learn translational perturbations using Caffe or PyTorch
- Random rotations of the ligand can be predicted by STNs but with weaker accuracy than translation using Caffe
- PyTorch model was not able to converge for rotation perturbations.
- Results are promising - further testing needs to be performed

Acknowledgements

AMIA
INFORMATICS PROFESSIONALS. LEADING THE WAY.

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Department of Computational and Systems Biology

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